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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/472,843	06/07/1995	ROLF J. MEHLHORN	028723-063	1044

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EXAMINER

KISHORE, GOLLAMUDI S

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 12/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/472,843	Applicant(s) Mehlhorn
	Examiner Gollamudi Kishore	Art Unit 1615
<i>-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --</i>		
Period for Reply		
A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE <u>three</u> MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.		
- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication. - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely. - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication. - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). - Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).		
Status		
1) <input checked="" type="checkbox"/> Responsive to communication(s) filed on <u>Oct 1, 2002</u>		
2a) <input checked="" type="checkbox"/> This action is FINAL. 2b) <input type="checkbox"/> This action is non-final.		
3) <input type="checkbox"/> Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under <i>Ex parte Quayle</i> , 1935 C.D. 11; 453 O.G. 213.		
Disposition of Claims		
4) <input checked="" type="checkbox"/> Claim(s) <u>46-65</u> is/are pending in the application.		
4a) Of the above, claim(s) _____ is/are withdrawn from consideration.		
5) <input type="checkbox"/> Claim(s) _____ is/are allowed.		
6) <input checked="" type="checkbox"/> Claim(s) <u>46-65</u> is/are rejected.		
7) <input type="checkbox"/> Claim(s) _____ is/are objected to.		
8) <input type="checkbox"/> Claims _____ are subject to restriction and/or election requirement.		
Application Papers		
9) <input type="checkbox"/> The specification is objected to by the Examiner.		
10) <input type="checkbox"/> The drawing(s) filed on _____ is/are a) <input type="checkbox"/> accepted or b) <input type="checkbox"/> objected to by the Examiner. Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).		
11) <input type="checkbox"/> The proposed drawing correction filed on _____ is: a) <input type="checkbox"/> approved b) <input type="checkbox"/> disapproved by the Examiner. If approved, corrected drawings are required in reply to this Office action.		
12) <input type="checkbox"/> The oath or declaration is objected to by the Examiner.		
Priority under 35 U.S.C. §§ 119 and 120		
13) <input type="checkbox"/> Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f). a) <input type="checkbox"/> All b) <input type="checkbox"/> Some* c) <input type="checkbox"/> None of: 1. <input type="checkbox"/> Certified copies of the priority documents have been received. 2. <input type="checkbox"/> Certified copies of the priority documents have been received in Application No. _____. 3. <input type="checkbox"/> Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)). *See the attached detailed Office action for a list of the certified copies not received.		
14) <input type="checkbox"/> Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e). a) <input type="checkbox"/> The translation of the foreign language provisional application has been received.		
15) <input type="checkbox"/> Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.		
Attachment(s)		
1) <input type="checkbox"/> Notice of References Cited (PTO-892)		
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)		
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____		
4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____		
5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)		
6) <input type="checkbox"/> Other: _____		

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DETAILED ACTION

The request for the extension of time and amendment filed on 10-1-02 are acknowledged.

Claims included in the prosecution are 46-65.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 46-65 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The limitation “independent of maintenance of a pH gradient across the liposome-membrane after entrapment of the chemical species” now introduced in claims 46 and 52 does not appear to have support in the specification originally filed and hence, deemed to be new matter.

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Claim Rejections - 35 U.S.C. § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 46-54, 57 and 61-64 are rejected under 35 U.S.C. 102(b) as being anticipated by Deamer (BBA, 1972) of record.

Deamer discloses a method of preparation of liposomes using instant method (note entire publication, page 270 in particular). The compounds loaded include are amines (note abstract and Method section). The method involves preparing liposomes with acidic pH and titrating them with a base to create a pH gradient and adding a basic amine.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that the primary focus of Deamer is to analyze the effects of pH gradient on fluorescent probes and that Deamer does not teach that the stability of the liposome is independent of maintenance of a pH gradient across the liposome membrane after entrapment of the chemical species or that this stability allows the animal to suffer "no long-term effects of the administration. These arguments are not found to be persuasive. First of all, instant claims are method of preparation claims and not method of administration claims and Deamer teaches the same process of preparation. Since it is the

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same process, whether Deamer analyzes or not or whether Deamer teaches the stability or not, these parameters will be the same in Deamer as in instant invention and applicant has not shown to be otherwise. The rejection is maintained.

5. Claims 46-54, 59 and 61-64 are rejected under 35 U.S.C. 102(b) as being anticipated by Cramer (BBRC, 1977) or Kano (BBA, 1978) already of record.

The references of Cramer and Kano disclose a method of loading substances using pH gradient (note the abstracts). The method involves the preparation of liposomes and lowering the pH of the external medium. The compounds loaded are acidic in nature (note the abstract and Materials and methods).

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant's arguments are similar to those put forth for the rejection over Deamer. In essence, applicant argues that Cramer teaches the physical chemistry involved in using a pH gradient to load certain simple ionizable molecules into a liposomes and that Kano teaches pyronine as a probe for monitoring the pH in the interiors of negatively charged liposomes and at the outer surface of positively charged liposomes. These arguments are not persuasive since as pointed out above, instant claims are process claims and the references teach the same process. The differences argued are not reflected in the claim language. The arguments on page 11 of applicant's response to the leakage upon

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administration to a host appear to be speculative in nature since there is no experimental evidence is presented.

Claim Rejections - 35 U.S.C. § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. Claims 46-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Deamer or Cramer or Kano cited above.

Deamer do not teach the establishment of the pH gradient by the addition of an acid. It is deemed however, to be within the skill of the art of chemistry that if the internal medium is basic one can only establish a gradient by the addition of a acidic substance (that is, altering the pH). Deamer does not teach instant drugs. However, Deamer teaches the concept of loading a chemical species into the liposomes using a pH gradient. It would have been obvious to one of ordinary skill in the art to load any drug with the expectation of similar loading since Deamer teaches the principle of loading.

Cramer and Kano do not teach the establishment of the pH gradient by the addition of a base. It is deemed however, to be within the skill of the art of chemistry that if the internal medium is acidic one can only establish a gradient by the addition of a basic substance (that is, altering the pH). Cramer and Kano do not teach instant drugs. However,

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Cramer and Kano teach the concept of loading a chemical species into the liposomes using a pH gradient. It would have been obvious to one of ordinary skill in the art to load any drug with the expectation of similar loading since both references teach the principle of loading.

Applicant provides no additional arguments to the above rejections in their response. Applicant argues that it was only with the present invention that liposomes which could be injected into a rat *in vivo* for the delivery of drugs were obtained and recognized as such and that prior to these experiments, one would not have known whether such drug entrapped liposomes would wreak havoc on the biogenic amines that play a vital role in animal physiology. Applicant while admitting that as demonstrated in Deamer, catecholamines could be loaded into liposomes with pH gradients argue that until after applicant's *in vivo* experiments were performed, no one could have predicted that an animal would tolerate the injection of such catecholamine loaded liposomes because none of the cited references discloses or suggests liposomes which retain their stability in the absence of a pH gradient across the liposomal membrane. These arguments are not found to be persuasive since as pointed out before, instant claims are drawn to a method of preparation and not method or administration or method of treatment. With regard to the examiner's previous statement that differences argued are not reflected in the claims, applicant argues that the amendments now will overcome the rejection. However, since the amendments made are in terms of functional language and not in terms of specific

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components (such as the lipids making up the liposomes, or the chemical species loaded or the buffers) or method steps which distinguish the instant method from the prior art method, the rejection is maintained. It is interesting to note that applicant states on page 14 of the specification (see line 5 et seq.), ‘that after incorporation of the chemical will remain in the vesicle for 15 minutes to several hours depending upon the chemical ----’. This statement does not appear to reflect the ‘stability’ as argued by applicant. It would appear from this statement that the stability depends on the nature of the drug loaded.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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9. **Any inquiry concerning this communication or earlier communications from the examiner should be directed to *G.S. Kishore* whose telephone number is (703) 308-2440.**

The examiner can normally be reached on Monday-Thursday from 6:30 A.M. to 4:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *T.K. Page*, can be reached on (703)308-2927. The fax phone number for this Group is (703)305-3592.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [thurman.page@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

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**Any inquiry of a general nature or relating to the status of this application should
be directed to the Group receptionist whose telephone number is (703)308-1235.**

GSK
Gollamudi S. Kishore, Ph. D

Primary Examiner

Group 1600

gsk

December 19, 2002